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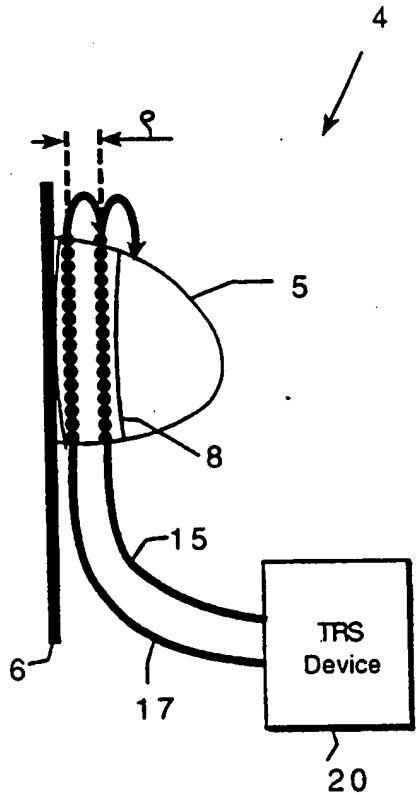
(54) Title: EXAMINATION OF BREAST TISSUE USING TIME-RESOLVED SPECTROSCOPY

(57) Abstract

A method and a system (4) for breast tissue examination includes a time-resolved spectroscopy apparatus (20; 20A; 20B), a support (8; 9; 11; 12; 13) with an input port (14) and an output port (16) separated by a selected distance is positioned relative to the examined breast. Locations of the input and output ports are selected to examine a tissue region of the breast. A light source (32; 34; 60) generates pulses of electromagnetic radiation of a selected wavelength in the visible or infrared range. The pulses of duration on the order of a nanosecond or less are introduced into the breast tissue at the input port (14) and detected over time at the detection port (16). Signals corresponding to photons of detected modified pulses are accumulated over time. Values of the scattering coefficient or the absorption coefficient of the examined breast tissue are calculated based on the shape of the modified pulses. The examined breast tissue is characterized based on the values of the scattering coefficient or the absorption coefficient. Absorbing or fluorescing contrast agents may be introduced into the examined tissue. The system may be adapted for use with x-ray mammography, needle localization procedure or MRI mammography.



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EXAMINATION OF BREAST TISSUE USING TIME-RESOLVED SPECTROSCOPY

Background of the Invention

The invention features a time-resolved spectroscopic method and apparatus for breast tissue examination.

Breast cancer is among the most common and the most feared malignancies in women. It has an unpredictable course, the treatment is frequently physically and emotionally draining and the risk of metastatic spread persists for many years. Due to its high occurrence rate, routine breast cancer screening, which includes physical examination and x-ray mammography, plays an important role in current health care. X-ray mammography can detect over 90% of all masses and increases the 10-year survival rate to about 95% for patients with cancers solely detected by mammography. Although the modern mammography uses a low-dose of x-rays, it still involves some small risk of inducing cancers by the radiation. Other tests, such as magnetic resonance imaging (MRI) and gadolinium enhanced MRI, have been used successfully for detection of breast tumors and may be used routinely for screening in the future.

After a small suspicious mass is detected in the breast non-invasively, excisional biopsy is usually performed to exclude or diagnose malignancy. The biopsy specimen is removed under local anesthesia and is used for histopathological diagnosis. The statistics show that in about 75% of the excisional biopsies, the biopsied tissue is diagnosed to be benign. Thus, a majority of patients undergoes this unpleasant and costly procedure unnecessarily. Furthermore, it has been

suggested that the excisional biopsy may cause spreading of the malignant tumor cells.

Therefore, a non-invasive, relatively inexpensive technique that can detect and characterize breast tumors may find its place in today's health care, alone or in conjunction with the above-mentioned techniques.

Summary of the Invention

The invention features a system and a method for breast tissue examination using time-resolved spectroscopy.

In general, in one aspect, the method includes the following steps. A support that includes an input port and an output port separated by a selected distance is positioned relative to the examined breast. Locations of the input and output ports are selected to examine a tissue region of the breast. Light pulses of a selected wavelength and duration less than a nanosecond are introduced into the breast tissue at the input port and detected over time at the detection port. Signals corresponding to photons of detected modified pulses are accumulated over the arrival time of detected photons. Values of a scattering coefficient or an absorption coefficient of the examined breast tissue are calculated based on the shape of the modified pulses. The examined breast tissue is characterized based on the values of the scattering coefficient or the absorption coefficient.

In general, in another aspect, the method includes the following steps. A support that includes an input port and an output port separated by a selected distance is positioned relative to the examined breast. Locations of the input and output ports are selected to examine a tissue region of the breast. Light pulses of a selected wavelength and duration less than a nanosecond are introduced into the breast tissue at the input port and detected over time at the detection port. Signals

corresponding to photons of detected modified pulses are integrated over at least two selected time intervals separately spaced over the arrival time of the modified pulses. A value of an absorption coefficient of the examined breast tissue is calculated based on the shape of the modified pulses. The examined breast tissue is characterized based on the value of the absorption coefficient.

In this aspect, the method may include further steps. The detected photons are integrated over other selected time intervals separately spaced over the arrival time of the modified pulses. Time dependence of the light intensity is determined based on the number of photons integrated over each time interval, and a value of a scattering coefficient of the examined breast tissue is determined. The examined breast tissue is characterized based on the value of the scattering coefficient.

Preferred methods use the above-described steps and additional steps as follows.

The input port and the output port are moved to a different location to examine another tissue region of the breast. Values of the scattering coefficient or absorption coefficient are again determined by repeating the above-described steps for the newly selected tissue region. The tissue region is characterized using the additional values of the scattering coefficient or the absorption coefficient.

The above-described steps are performed over several tissue regions to examine the entire breast.

The characterizing step includes comparing the calculated values of the scattering or absorption coefficient with selected values of scattering or absorption coefficient, respectively.

The selected values of the scattering and absorption coefficient correspond to normal breast tissue, normal contralateral breast tissue or series of homogenous breast tumors.

The characterizing step includes comparing the calculated values of the scattering coefficient or the absorption coefficient with selected values of the scattering coefficient or the absorption coefficient, respectively.

When the characterizing step reveals that the examined tissue includes abnormal tissue further the steps are performed. Another location of the input port and the output port is selected to define a new tissue region proximate to the region having abnormal tissue. The values of the scattering coefficient or the absorption coefficient of the newly selected tissue region are determined by applying the corresponding steps. Abnormal breast tissue is localized by comparing values of the scattering coefficient or the absorption coefficient of different selected tissue regions. The type of the abnormal tissue may be determined by comparing values of the scattering coefficient or the absorption coefficient of the localized tissue to values of the scattering coefficient or the absorption coefficient corresponding to selected tissue masses.

The tissue masses include one of the following: carcinoma, fibroadenoma or fibrocystic tissue.

The size and location of the abnormal tissue region is determined.

When the characterizing step reveals that the examined tissue includes abnormal tissue further the steps are performed. A contrast agent exhibiting known optical properties at the selected wavelength is injected into the blood stream of the subject. Another location of the input port and the output port is selected to

define a new tissue region proximate to the region having abnormal tissue. The values of the scattering coefficient or the absorption coefficient of the newly selected tissue region are determined. The abnormal breast tissue is localized by comparing values of the scattering coefficient or the absorption coefficient of different selected tissue regions.

The type of the abnormal tissue may be determined by comparing values of the scattering coefficient or the absorption coefficient of the localized tissue to values of the scattering coefficient or the absorption coefficient corresponding to selected tissue masses comprising the contrast agent.

When the characterizing step reveals that the examined tissue includes abnormal tissue further the steps are performed. A contrast agent exhibiting known optical properties at the selected wavelength is injected into the abnormal tissue. A location of the input port and the output port is selected. The values of the scattering coefficient or the absorption coefficient of the newly selected tissue region are determined. The abnormal breast tissue is localized by comparing values of the scattering coefficient or the absorption coefficient of different selected tissue regions.

The type of the abnormal tissue may be determined by comparing values of the scattering coefficient or the absorption coefficient of the localized tissue to values of the scattering coefficient or the absorption coefficient corresponding to selected tissue masses comprising the contrast agent.

The contrast agent is a fluorescing material or absorbing material. The contrast agent is preferentially absorbed by the tissue mass.

The above described steps are performed in conjunction with x-ray mammography, MRI mammography or a needle localization procedure.

In another aspect, the invention features a system for performing the above-described method.

Brief Description of the Drawing

Fig. 1 depicts diagrammatically a time-resolved spectroscopic system for breast tissue examination.

Figs. 1A, 1B, 1C and 1D depict different embodiments an optical fiber support for breast tissue examination.

Fig. 2 depicts diagrammatically a single photon counting TRS apparatus arranged for breast tissue examination.

Fig. 3 depicts diagrammatically a TRS boxcar apparatus arranged for breast tissue examination.

Fig. 3A shows a timing diagram of the apparatus of Fig. 3.

Fig. 3B shows a typical time resolved spectrum collected by the apparatus of Fig. 3.

Fig. 4 depicts diagrammatically examination of breast tissue using a fluorescing contrast agent.

Figs. 4A and 4B depict diagrammatically examination of breast tissue using MRI and time-resolved spectroscopy.

Figs. 5A, 5B, 5C, 5D, 5E and 5F display values of the absorption coefficient and the scattering coefficient of normal breast tissue measured at different locations of the right breast and of the left breast.

Figs. 6A and 6B display values of the absorption coefficient and the scattering coefficient, respectively, of normal breast tissue for women of different ethnic background.

Description of the Preferred Embodiments

Fig. 1 depicts a breast tissue examination system 4 placed on a human breast 5 for breast tissue examination. The system includes an optical fiber support 8 with multiple input ports 14 and multiple output ports 16. Support 8 is placed around breast 5 so that input ports 14 and output ports 16 define irradiation locations and detection locations on the skin of breast 5, respectively. Connected to selected input and output ports are optical fibers 15 and 17, respectively. System 4 uses either a single photon tissue resolved apparatus 20A or a time resolved apparatus 20B using boxcar type integration.

Referring also to Figs. 1A, 1B, 1C and 1D, system 4 uses different types of the optical fiber supports designed to introduce and detect photons at selected locations and thus shape the optical field. The optical fiber supports are made of flexible or rigid materials and are shaped to accommodate breasts of different volumes. Furthermore, the inside surface of the supports may include material of known scattering and absorptive properties. The material is selected to either return back to the breast tissue photons escaping through the skin (i.e., a low absorber and high scatterer) or provide additional paths for the escaping photons to the detector (i.e., the material has substantially the same optical properties as normal breast tissue). The supports are designed for use with a time-resolved spectrophotometer (TRS) alone or in conjunction with x-ray mammography, MRI or a needle localization procedure. Specifically, fiberoptic support 9 shown in Fig. 1A includes three sets of the input and detection ports labeled 10a, 10b, and 10c. Sets 10a and 10c are used to measure control data and set 10b is used to examine a suspected mass 7. Furthermore, support 9

enables precise characterization of the distances between the three sets, between input ports 14 and detection ports 16 (ρ) and from the chest wall 6 to each set (d_n). Supports 11 and 12, shown in Figs. 1B, 1C and 1D, are used with x-ray mammography and needle localization procedure, respectively, and their functions are described below.

Referring to Fig. 2, a dual wavelength, time correlated single photon counting TRS apparatus 20A is connected to support 13 positioned on breast 5. Pulsed laser diodes 32 and 34 (model PLP-10 made by Hamamatsu, Japan), are driven by a 5 mW pulser 36 connected to a 100 MHz pulse generator 37, and generate light pulses on the order of 500 psec or less. The light from laser diodes 32 and 34 is electro-mechanically time shared using a 60 Hz vibrating mirror 33 and is coupled to one end of optical fiber 15. Optical fiber 15, which has about 200 μm diameter, alternatively conducts pulses of 754 nm and 810 nm light to input port 14. The introduced photons migrate in the examined breast tissue and some of them arrive at output port 16. Optical fiber 17 collects photons of the modified pulses from an area of about 10 mm^2 and transmits them to a PMT detector 40.

The output of PMT 40 is connected to a wide band amplifier 42 with appropriate roll-off to give good pulse shape and optimal signal to noise ratio. Output signals from amplifier 42 are sent to a high/low level discriminator 44, which is a pulse amplitude discriminator with the threshold for pulse acceptance set to a constant fraction of the peak amplitude of the pulse. Next, the discriminator pulses are sent to a time-to-amplitude convertor (TAC) 46. TAC 46 produces an output pulse with an amplitude proportional to the time difference between the start and stop pulses received from pulser 36. The TAC pulses (47) are routed by a

switch 48 to either a multichannel analyzer (MCA) 50 or an MCA 52. Switch 48 operates at 60 Hz and is synchronized with mirror 33. The photon emission, detection cycle is repeated at a frequency on the order of 10 MHz.

Each MCA collects only a single photon for each light pulse introduced to the tissue. Each MCA acquires and sums photons of only one designated wavelength and stores the corresponding pulse of a shape that depends on properties of the examined tissue. The pulses are preferably accumulated over about 2 to 3 minutes so that at least 10^5 counts are collected at the maximum of the pulse shape. The detected pulse shape is analyzed by a computer 56. Computer 56 is connected to pulse generator 37 and MCAs 50 and 52 via an interface module 54 and is adapted to control the entire operation of the system.

Alternatively, TRS apparatus 20 represents a boxcar TRS apparatus 20B, as shown in Fig. 3. A pulsed laser diode 60 is driven by a 5 mW pulser 62 connected to a 100 MHz pulse generator 64. Laser diode 60 generates a train of 100 ps light pulses of 754 nm wavelength coupled to optical input fiber 15. The light pulses are introduced to breast tissue at input port 14. The introduced photons migrate in the examined tissue and a portion of them arrives at an output port 16. In the migration process, the input pulse has been modified by the scattering and absorptive properties of the examined tissue. Photons arriving at detection port 16 are transmitted by optical fiber 17 to a detector 66, (for example, Hamamatsu photomultipliers R928, R1517, MCP R1712, R1892).

The output of detector 66 is amplified in a wide band preamplifier/impedance changer 67 and coupled to a boxcar integrator 68. Integrator 68 activated by a pulse gate 73 collects all arriving photons over a

predetermined time interval 75, as shown in Fig. 3A. The integrator output (78) is sent to computer interface module 80 and computer 82. Computer 82 stores the total number of counts detected during the collection interval of integrator 68.

Integrator 68 includes a trigger 70, which is triggered by a signal 63 from pulser 62. Trigger 70 activates a delay gate 72 which, in turn, starts counting of all detected photons during the time interval specified by a gate width 74. Output from a gate width normalizer 76 is an analog signal or a digital signal representing all photons that arrived at detection port 16 during the preselected gate width interval (75). A suitable integrator is a boxcar SR 250 manufactured by Stanford Research Systems.

Depending on the application, computer 82 sets the delay time (71) of delay gate 72 and the gate width time (75) of gate width circuit 74. Gate width normalizer 76 adjusts the width of the integration time depending on the detected signal level. The gate width may be increased logarithmically for signals at $t>>t_{max}$, wherein the detected number of photons decreases exponentially; this increases the signal-to-noise ratio. Furthermore, computer 82 can scan the integration gate widths over the whole time profile of the detected pulse. By scanning the delay times (71) and appropriately adjusting the gate widths (75), the computer collects data corresponding to the entire detected pulse. Subsequently, computer 82 calculates the shape (85) of the detected pulse and stores the time dependent light intensity profile I(t).

The pulse shape, I(t), detected either by apparatus 20A or apparatus 20B possesses information about the scattering and absorptive properties of the examined breast tissue and is used to determine the scattering and absorption coefficients. Referring to

Fig. 3B, a test measurement was performed on apparatus 20A and found that due to a somewhat slow response time, the detector broadens the reflectance profile, as seen on spectrum 86. Thus the experimental spectra (87) are deconvoluted to separate the instrumental response from the profile dispersion due to the diffusion. The deconvolution yields about 6% increase in the value of μ_a and about 23% decrease in the value of μ_s.

The examined tissue region is defined by the distribution of photon pathlengths forming an optical field in the tissue. The size and shape of the optical field is a function of the input-output port separation (ρ) as well as the optical properties of the tissue (i.e., absorption coefficient, μ_a, scattering coefficient, μ_s, and the mean cosine of anisotropic scattering, g). The general diffusion equation is used to describe the photon migration in tissue, as analyzed by E.M. Sevick, B. Chance, J. Leigh, S. Nioka, and M. Maris in Analytical Biochemistry 195, 330 (1991), which is incorporated by reference as if fully set forth herein. The diffusion equation is solved for the intensity of detected light in the reflectance geometry, $R(\rho,t)$, or the transmittance geometry $T(\rho,d,t)$. In the reflectance geometry, in a semi-infinite media with the separation of the input and output ports on the order of centimeters, the absorption coefficient is a function of the reflectance spectrum as follows:

$$\frac{d}{dt}\log_e R(\rho,t) = \frac{-5}{2t} - \mu_a c + \frac{\rho^2}{4Dct} \qquad (1)$$

For $t \to \infty$ the absorption coefficient μ_a is determined as follows:

$$\lim_{t\to\infty}\frac{d}{dt}\log_e R(\rho,t) = -\mu_a c \qquad (2)$$

wherein ρ is the separation between input and detection ports and c is speed of light in the medium. However, it is difficult to measure the at $t>>t_{max}$ because in this region the data show substantial noise. Thus, to measure μ_a at $t>>t_{max}$, requires determination of the pulse shape at a high number of counts.

If the approximation of infinite time is not valid, Eq. 1 can be rewritten to obtain μ_a as follows:

$$\mu_a c = -\frac{d}{dt}\log_e R(\rho,t) + \frac{\rho^2}{4Dct} - \frac{5}{2t} \qquad (3)$$

The value for D can either be the average value obtained from numerical simulations or a value specific to the type of tissue being measured.

The effective scattering coefficient $(1-g)\cdot\mu_s$ is determined as follows:

$$(1-g)\mu_s = \frac{1}{\rho^2}(4\mu_a c^2 t_{max}^2 + 10 c t_{max}) - \mu_a \qquad (4)$$

wherein t_{max} is the delay time at which the detected reflectance time profile ($R(\rho,t) \equiv I(t)$) reaches maximum. After detecting the pulse shape corresponding to the examined tissue the computer calculates the absorption coefficient (μ_a), and the scattering coefficient (μ_s). The absorption coefficient is quantified by evaluating the decaying slope of the detected pulse, using Eqs. 2 or 3. The effective scattering coefficient, $(1-g)\cdot\mu_s$, is determined from Eq. 4.

The breast screening procedure starts by selecting a support with appropriate arrangement of input ports 14 and output ports 16. The absorptive and scattering properties of the tissue are measured for one set of

ports and then the optical field is transferred by using another set of ports. The entire breast is examined by selecting sequentially different ports. In the reflection geometry, the optical field can be represented by a three dimensional "banana-shaped" distribution pattern or, in the transmission geometry, a "cigar-shaped" distribution pattern. In the "banana-shaped" pattern, the shallow boundary is due to the escape of photons that reach the air-scatterer interface while the deeper boundary is due to attenuation of long path photons by the absorbers. The penetration depth of the photons is about one half of the port separation (ρ). During the screening procedure, the computer calculates μ_a and μ_s for the entire breast and compares the measured values with threshold values of μ_a and μ_s of normal tissue or series of μ_a and μ_s values of different homogeneous tumor types. As is shown in Figs. 5A through 5F, from one person to another there is some variation in μ_a and μ_s for normal tissue, but only a very small variation between the left breast and the right breast of the same person. Cancerous tissue, which is usually highly perfused, exhibits higher values of μ_a and μ_s than fibrous tissue. Normal tissue, which has a relatively high amount of fat, exhibits the lowest values of μ_a and μ_s.

Alternatively, instead of calculating μ_a and μ_s, the system can calculate an average pathlength of the migrating photons. From the detected and deconvoluted photon intensity profile, R(t), a mean pathlength of the distribution of pathlengths <L> is determined as follows:

$$\langle L \rangle = \frac{c}{n} \frac{\int_0^\infty I(t)\, t\, \partial t}{\int_0^\infty I(t)\, \partial t} \qquad (5)$$

wherein c is the speed of light in vacuum and $n \approx 1.36$ is the average refractive index of tissue.

If a breast tumor is outside of the optical field, it does not alter the banana-shaped distribution of pathlengths. As the optical field is moved closer to the breast tumor, which is a strongly absorbing mass, the photons that have migrated the farthest distance from the input and detection ports are eliminated by the absorption process. Since photons with the longest pathlengths are absorbed, the system detects reduction in the average pathlength. When the optical field is moved even closer to the mass, some of the detected photons now migrate around the mass without being absorbed; this is detected as lengthening of the distribution of pathlengths. Thus, the average pathlength measurement can reveal location of the breast mass.

In the screening process, the breast tissue is characterized by several tissue variables which may be used alone or in combination. System 20 measures the absorption coefficient, the scattering coefficient, blood volume or tissue oxygenation using one or more selected wavelengths. The wavelengths are sensitive to naturally occurring pigments or contrast agents that may be preferentially absorbed by the diseased tissue. Suitable naturally occurring pigments are, for example, hemoglobin (Hb) or oxyhemoglobin ($Hb0_2$) sensitive to 754 nm and 816 nm, respectively.

Alternatively, suitable color dyes, such as cardio-green or indocyinin-green, may be injected to the blood system alone or bound to a vehicle such as a gadolinium contrast agent, which is preferentially absorbed by tumors in the first five to ten minutes. An appropriate wavelength is selected for the color dye, for example, cardio-green exhibits maximum absorption at 805 nm.

The computer can create "maps" of the breast by mapping the spacial variation of the measured values for μ_a, μ_s, blood volume or hemoglobin saturation. The resolution is enhanced when several tissue variables are mapped. The blood volume is measured using a pair of contrabestic wavelengths (e.g., 754 nm and 816 nm) or the isobestic wavelength (i.e., 805 nm). The hemoglobin saturation (Y) is measured at two wavelengths (e.g., 754 nm and 816 nm) and is calculated by taking the ratio of absorption coefficients at these wavelengths and then using the following equation:

$$Y(X100\%) = \frac{38 - 18\frac{\mu_a^{754}}{\mu_a^{816}}}{25 + 3\frac{\mu_a^{754}}{\mu_a^{816}}} \qquad (6)$$

wherein the coefficients are determined from the extinction values of hemoglobin at 754 nm and 816 nm that are $\varepsilon_{Hb} = 0.38\ cm^{-1}\ mM^{-1}$, $\varepsilon_{Hb} = 0.18\ cm^{-1}mM^{-1}$, respectively, and the difference in extinction coefficients between oxyhemoglobin and hemoglobin that are $\Delta\varepsilon_{HbO-Hb} = 0.025\ cm^{-1}\ mM^{-1}$ and $\Delta\varepsilon_{HbO-Hb} = 0.03\ cm^{-1}\ mM^{-1}$, respectively.

In another preferred embodiment, TRS apparatus 20 is used in combination with x-ray mammography. The combined procedure is performed if a suspected mass is detected by the above-described optical method, x-ray mammography or other screening method.

Referring to Fig. 1B, breast 5 is compressed in either a horizontal or vertical position between an x-ray film case 90 with the x-ray film and a support 11 with input ports and output ports located on a grid. An x-ray mammogram is taken to determine location of suspected mass 7 relative to the grid. Suitable input port 14 and output port 16 are selected so that the introduced

optical field 92 encompasses mass 7. Then, TRS apparatus 20A or 20B is used to measure μ_a, μ_s, blood volume or oxygen concentration of the examined tissue using the above-described techniques. The measured values are again compared to the values corresponding to normal tissue or different types of diseased tissue to characterize the mass. If an unequivocal result is obtained, exploratory excisional biopsy is not needed.

In another preferred embodiment, TRS apparatus 20 is used in combination with the needle localization procedure. The needle localization procedure locates the mass that is then examined by system 4. Furthermore, a needle used in the needle localization procedure may introduce an optical fiber directly to mass 7.

Referring to Figs. 1C and 1D, breast 5 is compressed between x-ray film case 90 and a support 12 with input ports and output ports located on a grid and a centrally located opening for needle 94 or 98. One or more x-ray mammograms are taken to determine the location of suspected mass 7 relative to the grid and to the needle opening. The needle is inserted into the breast and the needle tip is positioned in the center of mass 7. Additional x-ray mammograms may be taken to verify or adjust the position of the needle.

As shown in Fig. 1C, if the needle is used only to localize mass 7, input port 14 and output port 16 are selected so that their separation is equal or larger than two times the depth of mass 7. This separation assures that the introduced optical field 96 encompasses mass 7. After needle 94 is positioned, a tiny wire is inserted into the mass and left there for marking purposes. TRS apparatus 20 measures μ_a, μ_s, blood volume or oxygen concentration of the examined tissue using the above-described techniques. The measured values are again compared to the values corresponding to normal tissue and

different types of diseased tissue, and the tissue of mass 7 is characterized.

As shown in Fig. 1D, needle 98 locates an end 99 of optical input fiber 15 directly inside mass 7. The optical fiber with a diameter of about 100 μm or less is threaded inside needle 98. End 99 is slightly extended from the needle so that the introduced photons are directly coupled to mass 7. The location of detection port 16 defines optical field 100. In this arrangement, all detected photons migrate in the targeted tissue; this increases the relative amount of the targeted tissue being examined and thus increases the resolution of the system. To compare tissue of mass 7 with normal tissue, the same geometry of the input port and the detection port is used to measure the optical properties of the contralateral breast. Alternatively, in the same breast, needle 98 is moved outside of mass 7 so that the positions of end 99 and detection port 16 define an optical field completely removed from mass 7. To characterize the mass, the values of μ_a and μ_s measured for mass 7 are compared either to the values of normal tissue measured in the same arrangement or to values of different types of diseased tissue.

In another embodiment, detection contrast is enhanced using fluorescing contrast agents. A tumor is permeated with the fluorescing contrast agent that has a decay time of less than 1 nsec, and the labeled tumor is then examined using a TRS device 20. Suitable agents emit fluorescing radiation in the range of 800 nm to 1000 nm, for example, carbocyanene dyes or porphorin compounds.

Referring to Fig. 4, the fluorescing contrast agent is injected to the blood system alone or bound to a vehicle, such as a gadolinium contrast agent, which is initially preferentially absorbed by a breast tumor.

Alternatively, the fluorescing agent is injected directly into the tumor. TRS device 20 generates 150 psec light pulses introduced into breast 5 at input port 14. The introduced photons of selected excitation wavelength reach tumor 7 and excite a fluorescing radiation 110, which propagates in all directions from tumor 7. The photons of fluorescing radiation 110 migrate in the examined breast tissue and some of them arrive at output port 16. Output port 16 has an interference filter that passes only photons at the wavelength of fluorescing radiation 110. Optical fiber 17 collects the transmitted photons, which are delivered to the PMT detector. System 4 may detect fluorescing radiation 110 at several output ports at the same time or move the ports to different positions on the fiber optic support.

TRS device 20 detects the pulses of fluorescing radiation 110; the shape of these pulses depends on the decay time of the fluorescing agent and optical properties of both the tumor tissue and the normal breast tissue.

In another embodiment, referring to Figs. 4A and 4B, TRS apparatus 20 is used in combination with MRI. MRI examined the breast with or without using a rare earth contrast agent. A network of surface coils 112 is cooperatively arranged with a fiberoptic support 114, which is constructed for use with MRI. The network of coils 112 and support 114 are appropriately located around the examined breast. At the same time as the MRI data are collected, TRS apparatus 20 collects the optical data. If an abnormal mass is detected, the MRI identifies the size and location of the mass. The optical data are then used to characterize the mass. Optical contrast agents may be used alone or in combination with the rare earth contrast agents, as described above.

EXPERIMENTS:

Preliminary experiments were conducted under a pre-approved protocol and after receiving informed consent of women with normal breast tissue and of women having a mass detected in their breast.

The examination of normal breast tissue was performed at several different locations of the right and left breast of the same woman. Referring to Figs. 2 and 3, letters RR, LR, LR and LL denote the right and left breast and the right and left breast side where the input and detection ports were located, respectively. Figs. 5A and 5B summarize the absorption coefficient (μ_a) and the scattering coefficient ($\mu_s' = (1-g)\cdot\mu_s$), respectively, measured on the right and left breast at a separation ρ = 6 cm. The values of μ_a and μ_s' for the right breast are identical to the values for the left breast within the measurement error. Figs. 5C and 5D summarize μ_a, μ_s', respectively, for the tissue on the left side and the right side of each breast, and Figs. 5E and 5F summarize μ_a, μ_s', respectively, for the tissue located at different distances from the chest wall. The data shown in Figs. 5A through 5F confirm that there is no significant difference in the optical properties measured over the entire breast.

The examination of normal breast tissue also measured differences in the optical properties corresponding to the volume of the breast, type of the breast tissue, the age of the woman and ethnic background. Based on the decreasing X-ray background absorption, the breast tissue was categorized as "dense", "fatty", or a "mixture" of the two tissue types. The values of μ_a and μ_s' of "fatty" tissue are lower than for "dense" tissue, which has a higher fibrous content. Since the shape of the breast varies, it was difficult to

categorize precisely the breast volume. For the volume measurement, the breast was stabilized on a plate and the length was measured from the chest to the end of the breast. The width and the thickness were measured at approximately 1 cm from the chest. Tissue of a large volume breast exhibits lower values of μ_a and μ_s' than that of a small volume breast. The same trend is observed for women above the age 50 when compared to women below 50. Figs. 6A and 6B display values of μ_a and μ_s', respectively, for Caucasians and African-Americans. Normal breast tissue of Caucasians and African-Americans exhibits substantially the same optical properties except for the values of μ_s' measured at the 4 cm separation. Since the skin forms a higher relative percentage of the examined tissue at a smaller separation of the input and output ports, the lower values of μ_s' may be due to a lower scattering coefficient of the skin with more pigment.

In all measurements, a smaller separation of the input and output ports yielded larger values of μ_a and μ_s' than a larger separation of the ports. This differences can be explained by violation of the semi-infinite boundary conditions at the smaller separations, i.e., a larger escape of photons through the tissue surface before they are collected by optical fiber 17. Furthermore, this dependence exists since the slope of the photon decay was measured not sufficiently far from the peak of the reflectance data as expressed in Eqs. 1, 2 and 3. This problem arises due to a low photon count of approximately 10,000 counts at the peak. Thus the measured data have a low signal to noise ratio and a reliable reflectance data can not be taken at $t>>t_{max}$. The corresponding error in the absorption coefficient, $E(\rho,t)|_{abs}$, is determined using Eq. 7.

$$E(\rho,t)/_{abs} = \frac{1}{c}[-\frac{5}{2t} + \frac{\rho^2}{4DCT}] \quad (7)$$

The error of scattering coefficient, $E(\rho,t,\mu_a)|_{sct}$, arises due to the error in the absorption coefficient. The corresponding error is determined using Eq. 8.

$$E(\rho,t,\mu_a)/_{sct} = \frac{1}{3\rho^2}[4E(\rho,t)/_{abs}C^2t_{max}^2] - E(\rho,t)/_{obs} \quad (8)$$

The preliminary values of μ_a and μ_s' corrected for the error using Eqs. 7. and 8 are shown in Table 1.

TABLE 1

Separation (cm)	Mean μ_a	μ_a Error Adjusted	Mean μ_s'	Mean t_{max} (ns)	μ_s' Error Adjusted
4	0.029	0.020	16.2	1.55	14.1
5	0.023	0.021	11.4	1.9	10.9
6	0.019	0.022	9.5	2.3	10.1
7	0.017	0.021	7.9	2.7	8.7

The corrected values of mean μ_a for different separations, ρ, are substantially the same, but the corrected values of mean μ_s still are ρ dependent although their spread is reduced considerably.

The examination of a breast with abnormal tissue was performed substantially the same way as the above-described examination of normal breast tissue. The breast tissue was first characterized by x-ray mammography and the size and location of a mass was determined. The examined breast was compressed between x-ray film case 90 and a support 12, as shown in Fig. 1C. Input port 14 and output port 16 were selected so that mass 7 was located in optical field 96. .

The values of μ_a and μ_s' measured around tumor 7 (using input output port set 10b of Fig. 1A) were

compared to control data measured on the same breast (using input output port sets 10a and 10c of Fig. 1A). The measured data were also correlated with pathology information on abnormalities in the examined breasts. The abnormalities were divided into the following three categories: fibrocystic, Fibroadenoma, and Carcinoma. Furthermore, these three categories are subdivided according to the size of the tumors as follows: smaller in diameter than 1 cm, and equal or larger in the diameter than 1 cm. Preliminary data measured on over fifty patients show an increase in the values of both μ_a and μ_s' when compared with normal tissue but statistical significance has not been demonstrated.

Other embodiments are within the following claims:

1. A system for in vivo examination of breast tissue of a female subject, comprising:

a light source constructed to generate pulses of electromagnetic radiation of a selected wavelength in the visible or infra-red range, said pulses having duration on the order of a nanosecond or less,

a support, positionable relative to said breast, comprising

an input port and an output port separated by a selected distance, said distance specifying a volume of the examined tissue, said input port, constructed to define an irradiation location of said breast, adapted to introduce into the breast tissue said generated pulses of light of said selected wavelength, said output port constructed to define a detection location of said breast,

optical material, at least partially surrounding said tissue, for limiting escape of photons outside said tissue,

a detector constructed to detect over time photons of modified pulses that have migrated in said breast tissue to said output port and produce corresponding electrical signals,

a photon counter, connected to said detector, constructed to accumulate over time said electrical signals and determine a shape of said modified pulses, and

a processor adapted to calculate values of scattering coefficients or absorption coefficients of the examined breast tissue based on said shape of said modified pulses and determine a physiological property of the breast tissue based on said coefficients.

2. A system for in vivo examination of breast tissue of a female subject, comprising:

a light source constructed to generate pulses of light of a selected wavelength in the visible or infra-red range, said pulses having duration on the order of a nanosecond or less,

a support, positionable relative to said breast, comprising

an input port and an output port separated by a selected distance, said input port, constructed to define an irradiation location of said breast, adapted to introduce into the breast tissue said generated pulses of light of said selected wavelength, said output port constructed to define a detection location of said breast,

optical material, at least partially surrounding said tissue, for limiting escape of photons outside said tissue,

a detector constructed to detect over time, at said output port, photons of said modified pulses that have migrated in said breast tissue to said output port and produce corresponding electrical signals,

gated integrator and an integrator timing control adapted to integrate said photons over at least two selected time intervals separately spaced over the arrival time of said modified pulses; and

a processor adapted to calculate values of absorption coefficients of the examined breast tissue based on the number of photons integrated over each time interval and determine a physiological property of the examined breast tissue based on said coefficients.

3. The system of claim 2 wherein said gated integrator, said integrator timing control, and said processor are further adapted to determine a delay time (t_{max}) between the time a pulse is introduced and the time the intensity of detected into the tissue corresponding modified pulse has a maximum value, said processor being

further adapted to determine the effective scattering coefficient $(1-g)\cdot\mu_s$ of the examined tissue.

4. A system for in vivo examination of breast tissue of a female subject, comprising:

a light source constructed to generate pulses of electromagnetic radiation of a selected wavelength in the visible or infra-red range, said pulses having duration on the order of a nanosecond or less,

a support, positionable relative to said breast, comprising

an input port and an output port separated by a selected distance, said distance specifying a volume of the examined tissue, said input port constructed to define an irradiation location of said breast, said output port constructed to define a detection location of said breast,

optical material, at least partially surrounding said tissue, for limiting escape of photons outside said tissue,

a detector constructed to detect over time photons of modified pulses that have migrated in said breast tissue to said output port and produce corresponding electrical signals,

a photon counter, connected to said detector, constructed to accumulate over time said electrical signals corresponding to a shape of said modified pulses, and

a processor, connected to said photon counter, adapted to calculate values of a scattering coefficient or an absorption coefficient of the examined breast tissue by comparing said detected radiation to said introduced radiation, and determine a physiological property of the breast tissue based on said coefficients.

5. The system of claim 1, 2, 3 or 4 wherein said selected wavelength is sensitive to a contrast agent of

known optical properties, said contrast agent being injectable into tissue of said subject, and said detected photons of said pulses have been modified by said contrast agent and said tissue while migrating in said tissue to said output port.

6. A system for in vivo examination of tissue of a subject, comprising:

a light source constructed to generate pulses of electromagnetic radiation of a selected wavelength in the visible or infra-red range, said pulses having duration on the order of a nanosecond or less,

said selected wavelength being sensitive to a contrast agent of known optical properties, said contrast agent being injectable into tissue of said subject,

an input port, constructed to define an irradiation location of the examined tissue, adapted to introduce into the tissue said generated pulses of light of said selected wavelength,

an output port constructed to define a detection location of the examined tissue,

a detector constructed to detect over time photons of pulses modified by said contrast agent and said tissue while migrating in said tissue to said output port, said detector producing electrical signals corresponding to said detected photons,

a photon counter, connected to said detector, constructed to accumulate over time said electrical signals corresponding to a shape of said modified pulses, and

a processor, connected to said photon counter, adapted to calculate values of a scattering coefficient or an absorption coefficient of the examined tissue by comparing said detected radiation to said introduced radiation, and determine a physiological property of the tissue based on said coefficients.

7. A system for in vivo examination of tissue of a subject, comprising:

a light source constructed to generate pulses of electromagnetic radiation of a selected wavelength in the visible or infra-red range, said pulses having duration on the order of a nanosecond or less,

said selected wavelength being sensitive to a contrast agent of known optical properties, said contrast agent being injectable into tissue of said subject,

an input port, constructed to define an irradiation location of the examined tissue, adapted to introduce into the tissue said generated pulses of light of said selected wavelength,

an output port constructed to define a detection location of the examined tissue,

a detector constructed to detect over time photons of pulses modified by said contrast agent and said tissue while migrating in said tissue to said output port, said detector producing electrical signals corresponding to said detected photons,

gated integrator and an integrator timing control are adapted to integrate said photons over at least two selected time intervals separately spaced over the arrival time of said modified pulses; and

a processor adapted to calculate values of absorption coefficients of the examined breast tissue based on the number of photons integrated over each time interval and determine a physiological property of the examined breast tissue based on said coefficients.

8. The system of claim 1, 2, 3, 4, 5, 6 or 7 wherein said support is constructed to enable accurate selection of said irradiation locations and said detection locations relative to said breast, each said selection forming a defined relative geometry of said irradiation and detection locations.

9. The system of claim 8 wherein said support is constructed for cooperative use with x-ray mammography.

10. The system of claim 8 wherein said support is constructed for cooperative use with needle localization procedure.

11. The system of claim 10 wherein said support further comprises an opening adapted to accomodate a needle used in said needle localization procedure.

12. The system of claim 42 wherein said support is constructed for cooperative use with MRI mammography.

13. The system of claim 1, 2, 3, 4, 5, 6, 7 or 8 wherein said processor is further adapted to compare said calculated values of the scattering coefficient or the absorption coefficient to selected values of the scattering coefficient or the absorption coefficient, respectively.

14. The system of claim 5, 6, 7 or 8 wherein said contrast agent is preferentially absorbed in an abnormal tissue.

15. The system of claim 5, 6, 7 or 8 wherein said contrast agent is fluorescing when irradiated and said detector is adapted to detect fluorescent radiation.

16. The system of claim 15 wherein said detector includes a filter adapted to pass only said fluorescent radiation.

17. The system of claim 5, 6, 7 or 8 wherein said contrast agent is also magnetically active and suitable for MRI examination of breast tissue.

18. The system of claim 17 wherein said contrast agent includes a rare earth contrast agent.

19. The system of claim 18 wherein said contrast agent is preferentially absorbed by abnormal tissue.

20. The system of claim 1, 2, 3, 4, 5, 6, 7 or 8 wherein said contrast agent is preferentially absorbed in an abnormal tissue region.

21. A method for examination of breast tissue of a female subject using pulses of light of a selected wavelength, said method comprising the steps of:

(a) providing a support, positionable relative to the examined breast, comprising

an input port and an output port separated by a selected distance, said input port constructed to define an irradiation location of said breast, said output port constructed to define a detection location of said breast,

optical material, at least partially surrounding said tissue, for limiting escape of photons outside said tissue,

(b) selecting locations of said input and output ports to examine a tissue region of the breast,

(c) introducing into the breast tissue, at said input port, pulses of light of a selected wavelength in the visible or infra-red range, said pulses having duration on the order of a nanosecond or less,

(d) detecting over time, at said detection port, photons of modified pulses that have migrated in the breast tissue,

(e) accumulating, over arrival time of said detected photons, electrical signals corresponding to said detected photons of said modified pulses,

(f) calculating values of a scattering coefficient or an absorption coefficient of the examined breast tissue by comparing said detected radiation to said introduced radiation, and

(g) characterizing the examined breast tissue based on said values of the scattering coefficient or the absorption coefficient.

22. A method for examination of breast tissue of a female subject using pulses of light of a selected wavelength, said method comprising the steps of:

(a) providing a support, positionable relative to the examined breast, comprising

an input port and an output port separated by a selected distance, said input port constructed to define an irradiation location of said breast, said output port constructed to define a detection location of said breast,

optical material, at least partially surrounding said tissue, for limiting escape of photons outside said tissue,

(b) selecting locations of said input and output ports to examine a tissue region of the breast,

(c) introducing into the breast tissue, at said input port, pulses of light of a selected wavelength in the visible or infra-red range, said pulses having duration on the order of a nanosecond or less,

(d) detecting over time, at said detection port, photons of modified pulses that have migrated in the breast tissue,

(e) integrating said photons over at least two selected time intervals separately spaced over the arrival time of said modified pulses,

(f) calculating a value of an absorption coefficient of the examined breast tissue based on the number of photons integrated over each time interval, and

(g) characterizing the examined breast tissue based on said value of the absorption coefficient.

23. The method of claim 22 wherein said (e) and (f) steps further comprise:

integrating said photons over other selected time intervals separately spaced over the arrival time of said modified pulses,

determining the time delay (t_{max}) between the time a pulse is introduced into the tissue and the time the intensity of corresponding modified pulse has a maximum

value, based on the number of photons integrated over said time intervals, and

calculating a value of the effective scattering coefficient of the examined breast tissue.

24. A method for examination of tissue of a subject using pulses of light of a selected wavelength, said method comprising the steps of:

providing an input port and an output port separated by a selected distance, said input port constructed to define an irradiation location of said tissue, said output port constructed to define a detection location of said tissue,

selecting locations of said input and output ports to examine a tissue region of said subject,

injecting into the tissue a contrast agent of known optical properties at said selected wavelength,

introducing into the tissue, at said input port, pulses of light of a selected wavelength in the visible or infra-red range, said pulses having duration on the order of a nanosecond or less,

detecting over time, at said detection port, photons of pulses modified by said contrast agent and said tissue while migrating in said tissue to said output port,

accumulating, over arrival time of said detected photons, electrical signals corresponding to said detected photons of said modified pulses,

calculating values of a scattering coefficient or an absorption coefficient of the examined tissue by comparing said detected radiation to said introduced radiation, and

characterizing the examined tissue based on said values of the scattering coefficient or the absorption coefficient.

25. A method for examination of tissue of a subject using pulses of light of a selected wavelength, said method comprising the steps of:

(a) providing an input port and an output port separated by a selected distance, said input port constructed to define an irradiation location of said tissue, said output port constructed to define a detection location of said tissue,

(b) selecting locations of said input and output ports to examine a tissue region of said subject,

(c) injecting into the tissue a contrast agent of known optical properties at said selected wavelength,

(d) introducing into the tissue, at said input port, pulses of light of a selected wavelength in the visible or infra-red range, said pulses having duration on the order of a nanosecond or less,

(e) detecting over time, at said detection port, photons of modified pulses that have migrated in the tissue,

(f) integrating said photons over at least two selected time intervals separately spaced over the arrival time of said modified pulses,

(g) calculating a value of an absorption coefficient of the examined tissue based on the number of photons integrated over each time interval, and

(h) characterizing the examined tissue based on said value of the absorption coefficient.

26. The method of claim 25 wherein said (e) and (f) steps further comprise:

integrating said photons over other selected time intervals separately spaced over the arrival time of said modified pulses,

determining the time delay (t_{max}) between the time a pulse is introduced into the tissue and the time the intensity of the corresponding modified pulse has a

maximum value, based on the number of photons integrated over said time intervals, and

calculating a value of the effective scattering coefficient of the examined tissue.

27. The method of claim 21, 22, 23, 24, 25 or 26 further comprising the steps of:

moving said input port and said output port to a different location to examine another tissue region of the breast,

repeating steps (c) through (f) to determine values of the scattering or absorption coefficient of said newly selected tissue region, and

characterizing the examined breast tissue based on said values of the scattering coefficient or the absorption coefficient.

28. The method of claim 21, 22 or 23 further comprising, the step of:

injecting into the blood stream of said subject a contrast agent of known optical properties at said selected wavelength, wherein said detected photons of said pulses have been modified by said contrast agent and said tissue while migrating in said tissue to said output port.

29. The method of claim 24, 25, 26, 27 or 28 further comprising the step of comparing said calculated values of the scattering coefficient or the absorption coefficient to selected values of the scattering coefficient or the absorption coefficient, respectively.

30. The method of claim 29 wherein said contrast agent is preferentially absorbed by abnormal tissue.

31. The method of claim 29 wherein said contrast agent is fluorescing when irradiated, and said detecting step includes detecting fluorescent radiation.

32. The method of claim 31 wherein said detecting step includes detecting only said fluorescent radiation.

33. The method of claim 29 wherein said contrast agent is also magnetically active and said method is used with MRI.

34. The method of claim 33 wherein said contrast agent includes a rare earth contrast agent.

35. The method of claim 29 wherein said selected values of the scattering and absorption coefficient correspond to normal breast tissue.

36. The method of claim 29 wherein said selected values of the scattering and absorption coefficient correspond to normal contralateral breast tissue.

37. The method of claim 29 wherein said selected values of the scattering and absorption coefficient correspond to series of homogenous breast tumors.

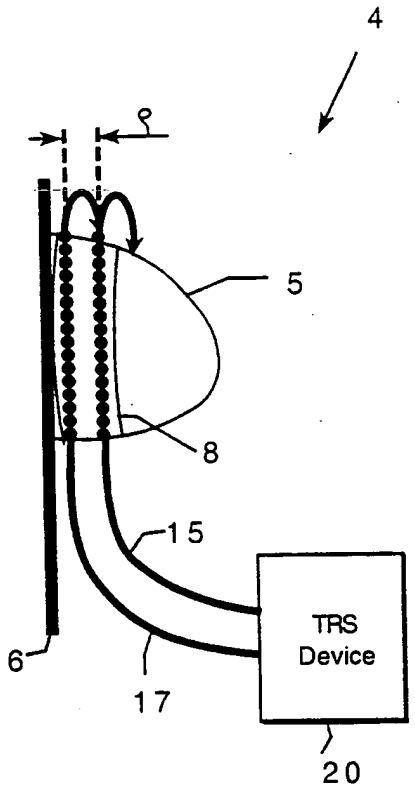

FIG. 1

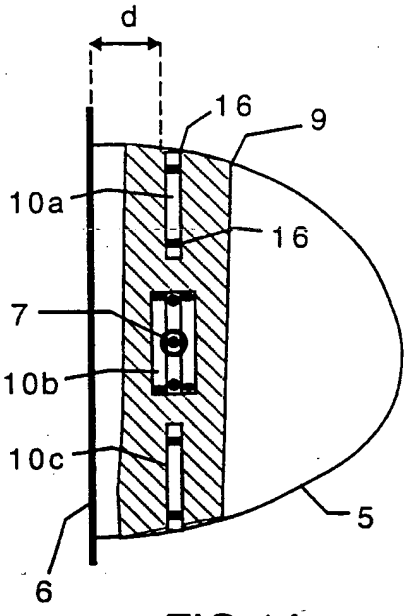

FIG.1A

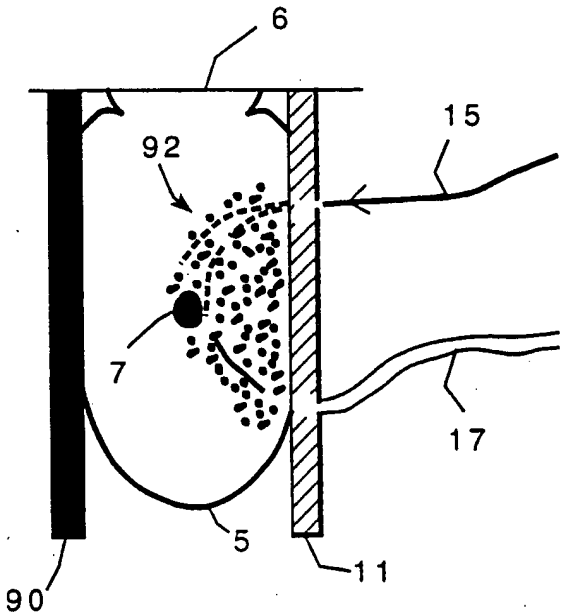

FIG.1B

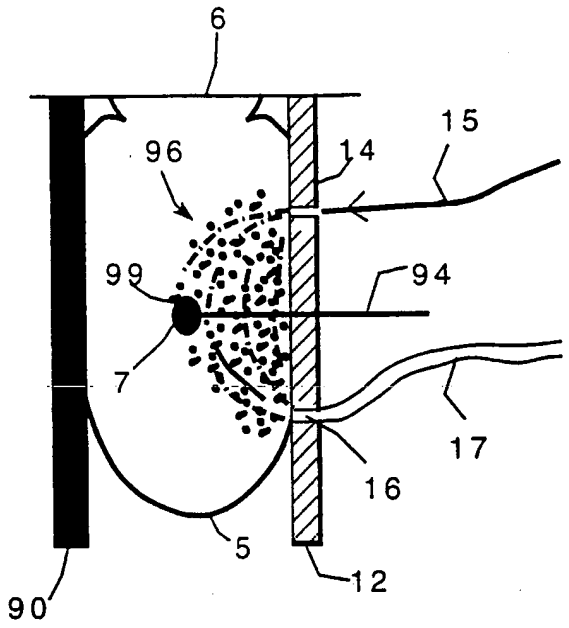

FIG.1C

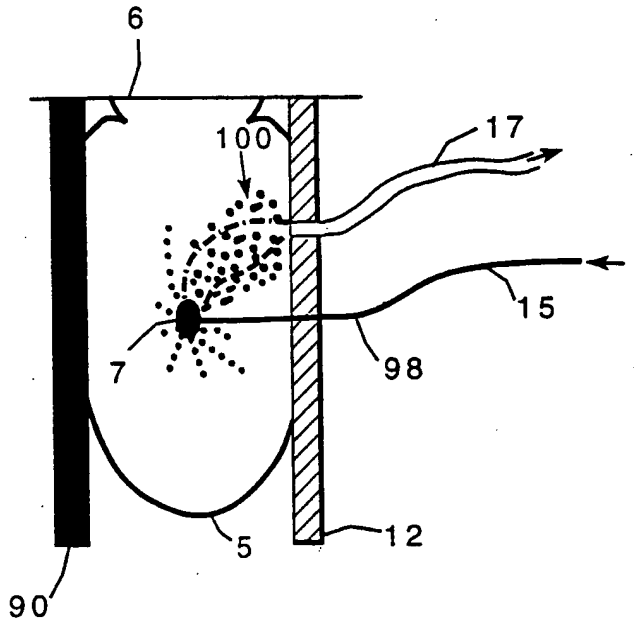

FIG.1D

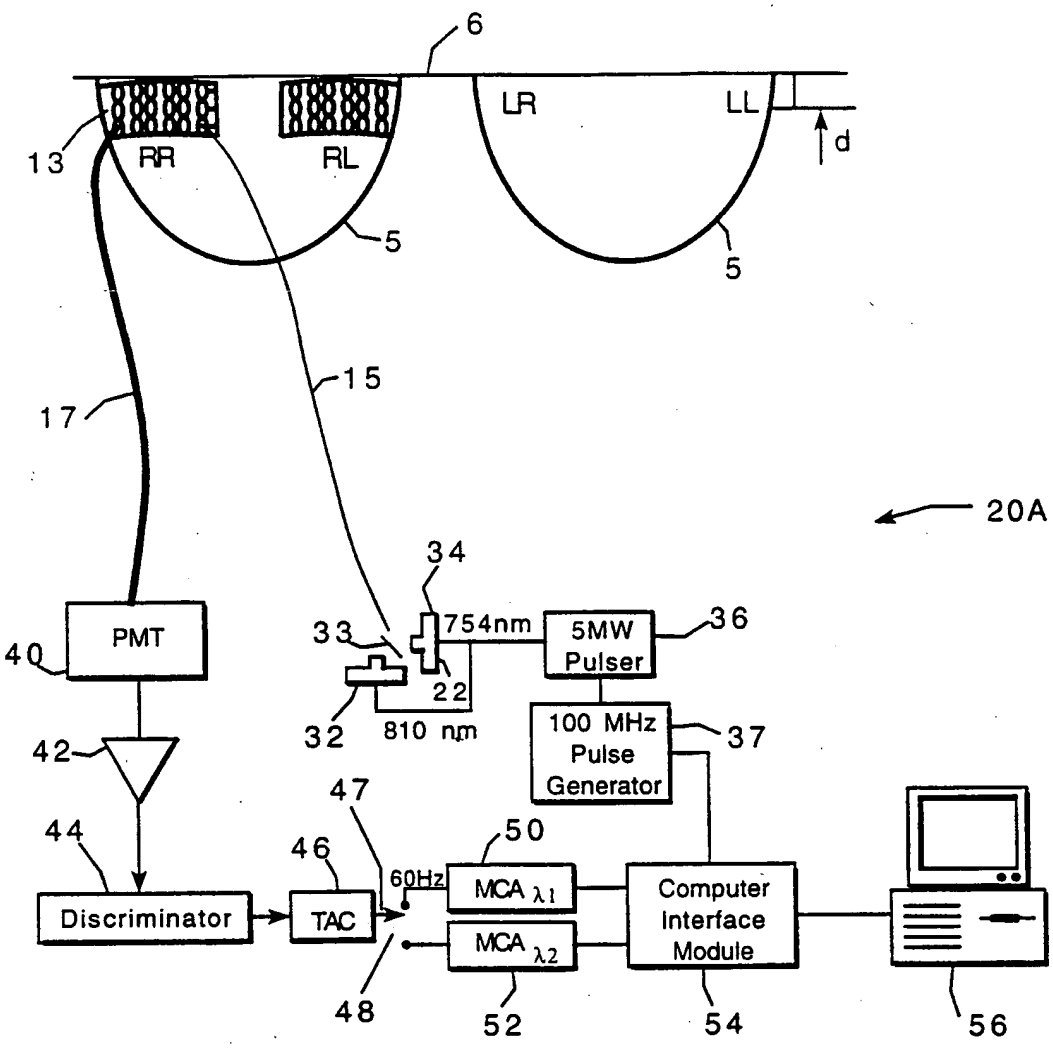
6
LR
LL
d
13
RR
RL
5
5
15
17
20A
34
754nm
5MW
Pulser
36
33
22
32
810 nm
100 MHz
Pulse
Generator
37
40
PMT
42
47
44
46
50
60Hz
MCA λ1
Computer
Interface
Module
Discriminator
TAC
MCA λ2
48
52
54
56

FIG. 2

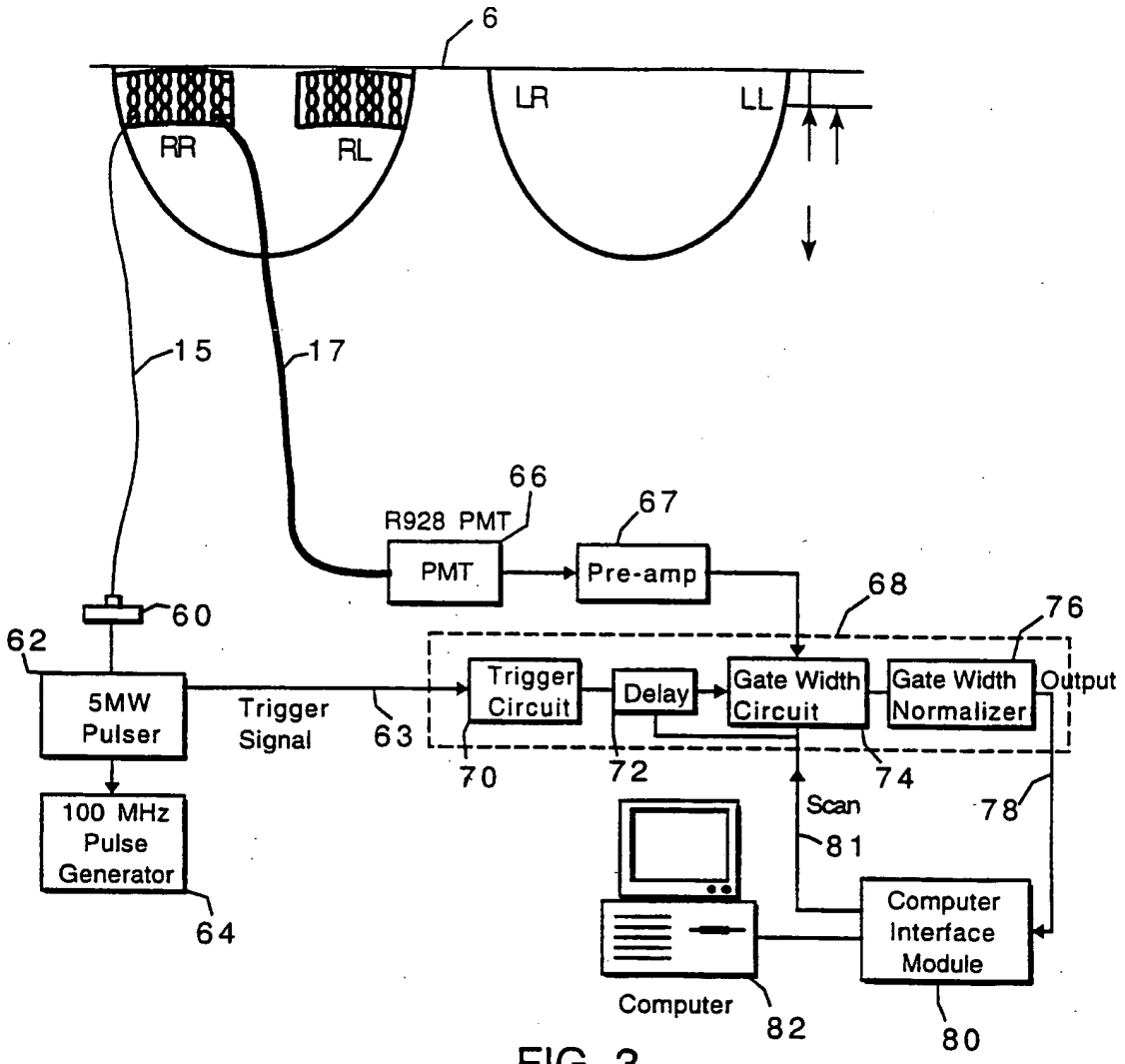
6
RR
RL
LR
LL
15
17
66
R928 PMT
PMT
67
Pre-amp
68
76
60
62
5MW Pulser
Trigger Signal
63
Trigger Circuit
Delay
Gate Width Circuit
Gate Width Normalizer
Output
70
72
74
78
Scan
81
100 MHz Pulse Generator
64
Computer Interface Module
Computer
82
80

FIG. 3

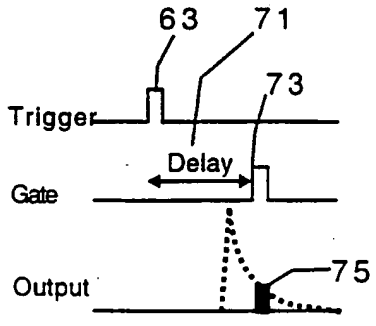
63
71
73
Trigger
Delay
Gate
Output
75

FIG. 3A

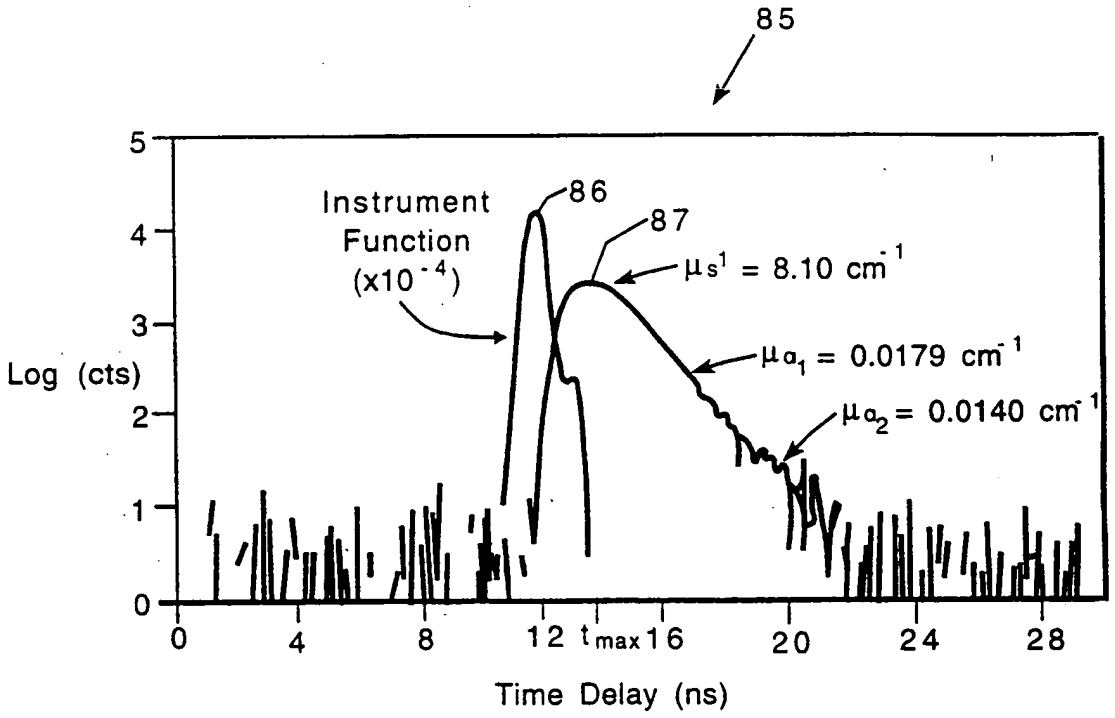
85
5
4
3
2
1
0
Log (cts)
Instrument
Function
(x10⁻⁴)
86
87
μs¹ = 8.10 cm⁻¹
μa₁ = 0.0179 cm⁻¹
μa₂ = 0.0140 cm⁻¹
0
4
8
12 tmax 16
20
24
28
Time Delay (ns)

FIG. 3B

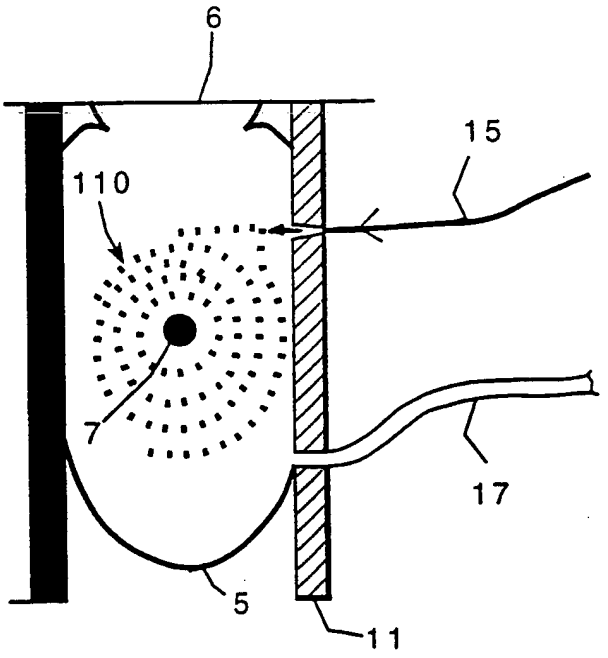

FIG. 4

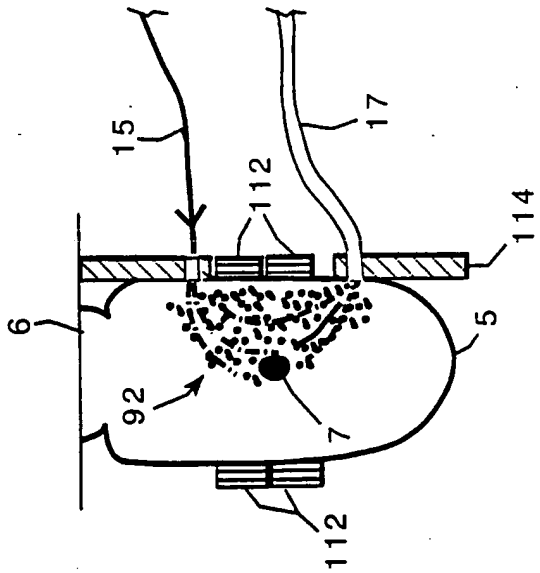

FIG. 4B

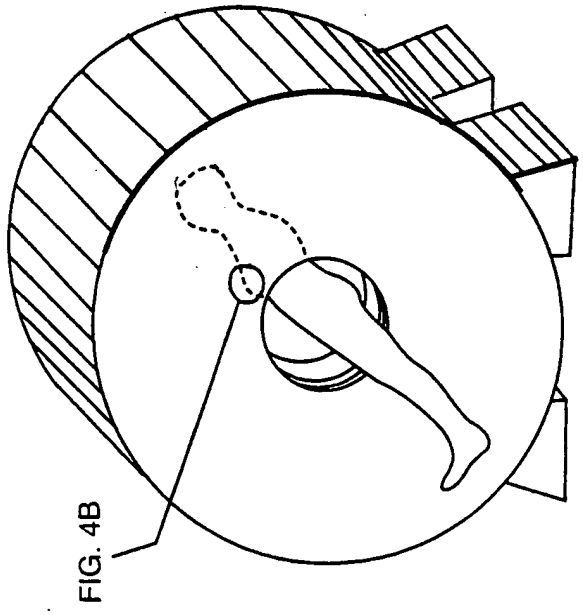

FIG. 4A

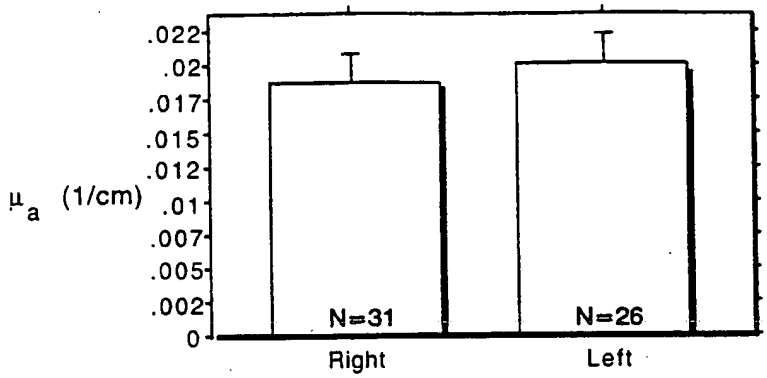

FIG. 5A

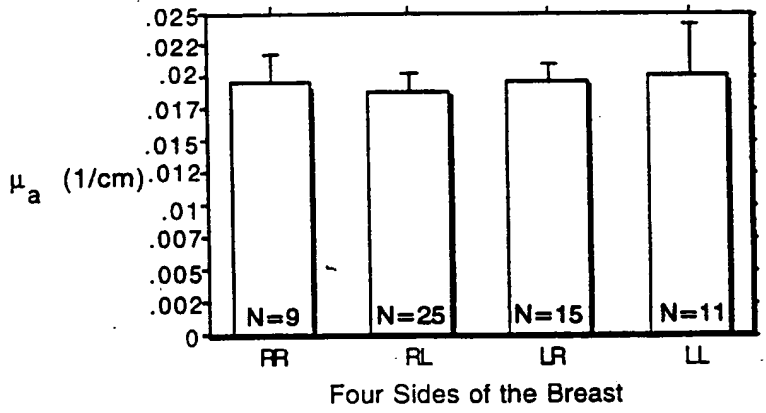

FIG. 5C

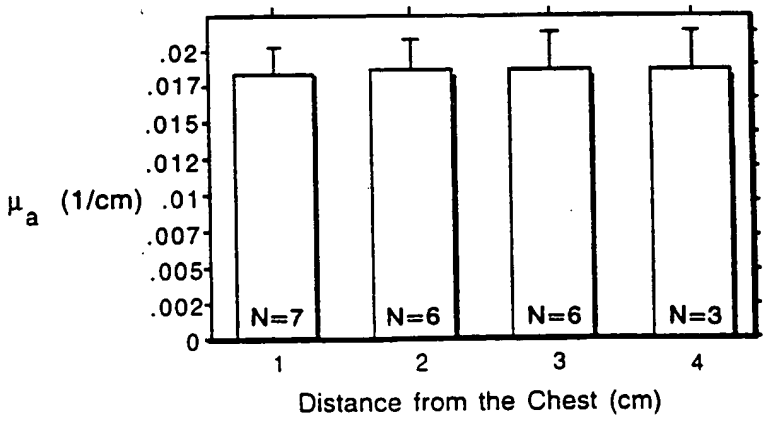

FIG. 5E

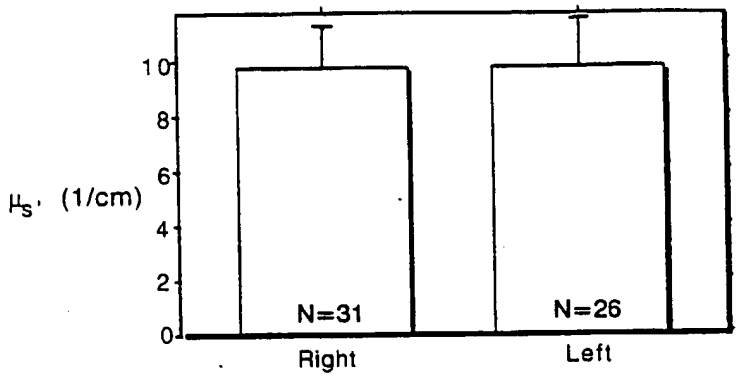

FIG. 5B

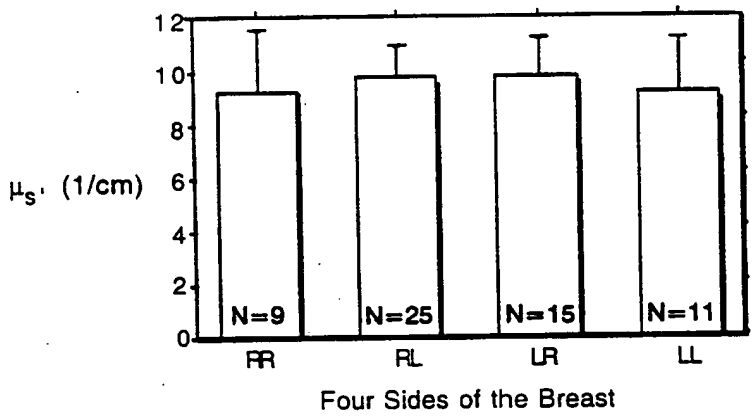

FIG. 5D

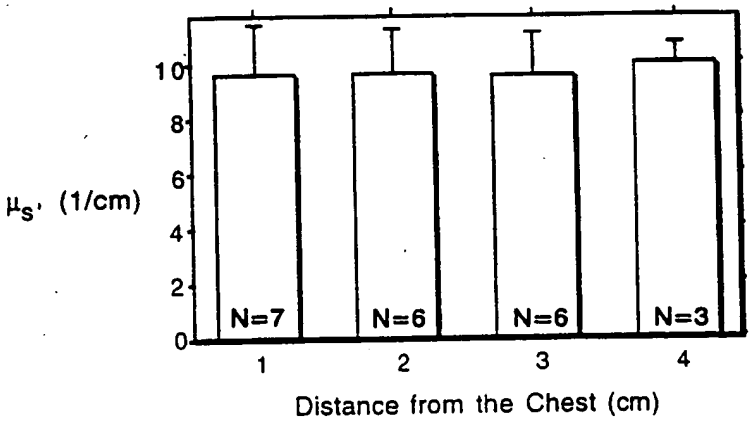

FIG. 5F

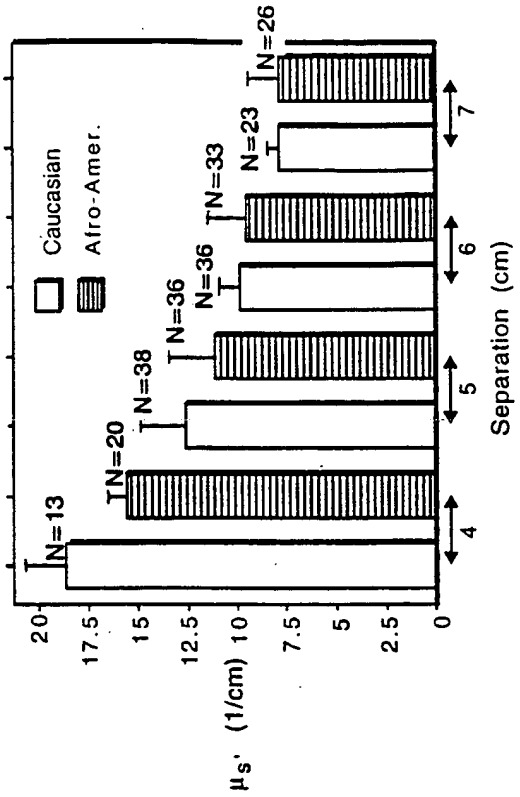
Caucasian
Afro-Amer.
N=13
N=20
N=38
N=36
N=36
N=33
N=23
N=26
20
17.5
15
12.5
10
7.5
5
2.5
0
4
5
6
7
μ_s' (1/cm)
Separation (cm)

FIG. 6B

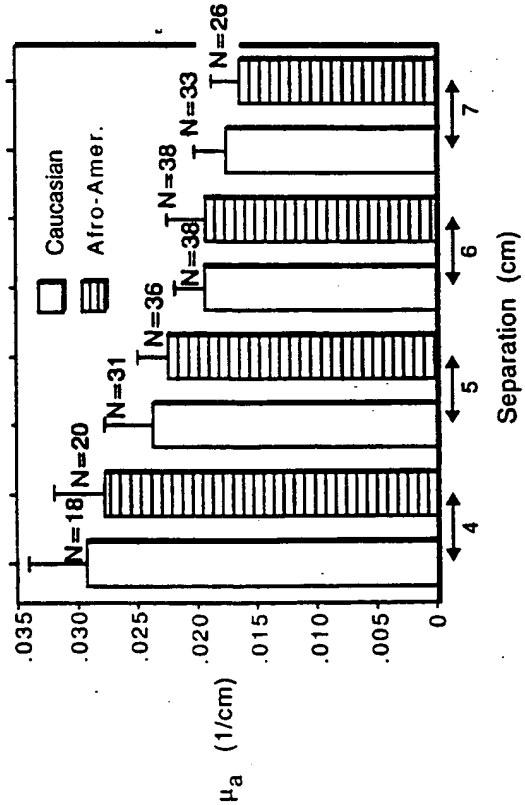
Caucasian
Afro-Amer.
N=18
N=20
N=31
N=36
N=38
N=38
N=33
N=26
.035
.030
.025
.020
.015
.010
.005
0
4
5
6
7
μ_a (1/cm)
Separation (cm)

FIG. 6A

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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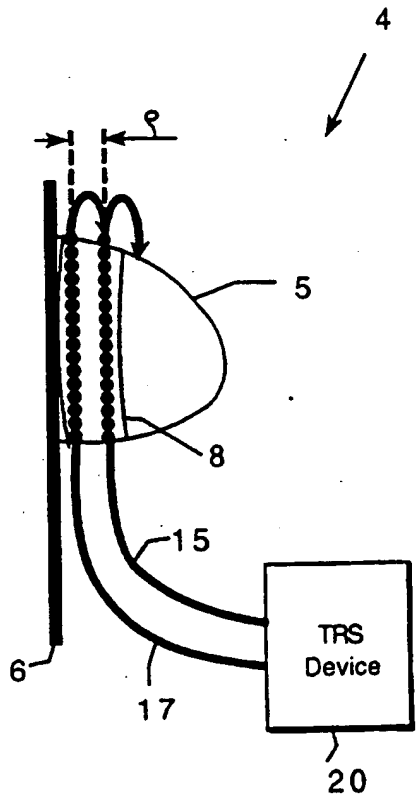
(54) Title: EXAMINATION OF BREAST TISSUE USING TIME-RESOLVED SPECTROSCOPY

(57) Abstract

A method and a system (4) for breast tissue examination includes a time-resolved spectroscopy apparatus (20; 20A; 20B), a support (8; 9; 11; 12; 13) with an input port (14) and an output port (16) separated by a selected distance is positioned relative to the examined breast. A light source (32; 34; 60) generates pulses of electromagnetic radiation of a selected wavelength in the visible or infrared range. The pules are introduced into the breast tissue at the input port (14) and detected over time at the output port (16). Signals corresponding to photons of detected modified pulses are accumulated over time. Values of the scattering coefficient or the absorption coefficient of the examined breast tissue are calculated based on the shape of the modified pulses. The examined breast tissue is characterized based on the values of the scattering coefficient or the absorption coefficient.



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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/07984

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y,E	US,A, 5,348,018 (ALFANO ET AL) 20 SEPTEMBER 1994 SEE ENTIRE DOCUMENT	1,2,3,4,21-23 ,27
Y	US,A, 5,090,415 (YAMASHITA ET AL) 25 FEBRUARY 1992, SEE ENTIRE DOCUMENT	1-4,21-23, 27

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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"P" document published prior to the international filing date but later than the priority date claimed

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
09 FEBRUARY 1995	28 FEB 1995

Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	RUTH S. SMITH
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0858

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/07984

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 12
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Please See Extra Sheet.

3. ☒ Claims Nos.: 8-11,13-20,29-37
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/07984

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

A61B 6/00

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

128/664,665

B. FIELDS SEARCHED
Minimum documentation searched
Classification System: U.S.

128/633,634,653.1,653.2,653.4,654,664,665

BOX I. OBSERVATIONS WHERE CLAIMS WERE FOUND UNSEARCHABLE
2. Where no meaningful search could be carried out, specifically:

Claim 12 depends from claim 42 which does not exist.